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EXAMINER

ARCHIE, NINA

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PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

ADVISORY ACTION

1. The amendment filed on 5/13/2009, in reply to the final rejection has been considered and will be entered but is not deemed to place the application in condition for allowance. Amendments and applicant's remarks have been considered but are not deemed persuasive for the reasons set forth below. Claims 6 and 21 are amended. Claims 1-7, 9-12, 13-21, and 28-30 are pending and under examination. Claims 8 and 22-27 have been cancelled.

Rejections Withdrawn

2. In view of the Applicant's amendment and remark following objections are withdrawn.
- a) Rejection of claims 1-5, 10, 13-21 and 28-30 under 35 U.S.C. 102(a) as being anticipated by Hook et al US Patent Application 20020169288 Date November 14, 2002 are withdrawn in light of applicant's argument.
 - b) Rejection of claims 1-3, 5, 10-11, 13-21 and 28 under 35 U.S.C. 102(b) as being anticipated by Costerton et al US Patent 5,312,813 Date May 17, 1994 are withdrawn in light of applicant's argument.
 - c) Rejection of claims 1-3, 5, 10-11, 13-19, 21, and 28-29 under 35 U.S.C. 102(b) as being anticipated by Wooley et al US Patent Application 20020091074 are withdrawn in light of applicant's argument.
 - d) Rejection of claims 6, 8, and 21 under 35 U.S.C. 112, second paragraph, wherein "said c-di-GMP or cyclic dinucleotide is c-di-GMP" are withdrawn in light of applicant's amendments (claims 6 and 21) and cancellation of claim 8.

Claim Rejections Maintained

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Enablement

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3. The rejections of claims 1-5, 10-16, and 28-30 under 35 U.S.C. 112, first paragraph failing to comply with the enablement requirement are maintained for the reason set forth in the previous office action. The claim(s) contain subject matter, which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Applicant's Arguments:

Applicants arguments filed in response to the 35 U.S.C. 112, first paragraph May 13, 2009 is carefully considered, but not found to be persuasive for the reasons below.

Applicants state that the examiner maintains this rejection because it appears that she is still taking the position that the claims encompass any type of derivative of a cyclic dinucleotide (i.e., cyclic dinucleotide analogue), although the declaration attached to the amendment of October 8, 2008 and the specification are limited to specific cyclic dinucleotides and that the examiner also states that the claims are drawn to encompass any genus of microbial pathogens in which the specification is only limited to *Staphylococcus aureus*. Applicants state that at the personal interview of August 4, 2008, when the inventor David Karaolis indicated that he had post-filing experimental data showing enablement in gram positive and gram negative bacteria, a fungus (fungal parasite of humans) and a viral pathogen Examiner Navarro indicated that this would be viewed very favorably in satisfying enablement, in particular since applicant proposed to recite for only "cyclic dinucleotides" which would not encompass analogues of cyclic dinucleotides. Applicants state that it was further discussed that the *Staphylococcus aureus* experimental results already presented in the present specification provide enablement for a gram positive bacteria and that if the applicant can show in declaration form positive results in a single microbial species in each of gram negative bacteria, fungi and viruses, then such a declaration would likely be sufficient to overcome this enablement rejection.

Applicants state that the executed 1.132 declaration submitted with the amendment of October 8, 2008, presented experimental results demonstrating that c-di-GMP significantly inhibits microbial colonization, virulence and infection against intranasal (i.n.) or intraperitoneal (i.p.) challenge with various microbial pathogens, including *Klebsiella pneumoniae* (a gram negative bacteria as opposed to *S. aureus* which is gram positive), *Streptococcus pneumoniae* (a gram positive bacteria), *Pneumocystis carinii* (fungal parasite/pathogen), and Respiratory

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Syncytial Virus (RSV, a viral pathogen). The examples of microbial pathogens span a wide range within the genus of microbial pathogens, which would lead one of ordinary skill in the art to readily believe and expect that the presently claimed methods would be applicable to the genus of microbial pathogens. As positive experimental results are found for such a diverse group of microbial pathogens and for various different cyclic dinucleotides, there is no reason for one of ordinary skill in the art to doubt that the presently claimed methods using cyclic dinucleotide would not work against microbial pathogens in general and therefore be enabled to those of skill in the art.

Examiner's Response to Applicant's Arguments:

In response to applicant's statement, as stated in the previous office action, the method as instantly claimed encompasses all dinculeotides. The 1.132 Declaration of October 8, 2008 was fully considered. However, based on the limited number of cyclic dinucleotides disclosed in the specification, which said cyclic dinucleotides were properly described is not persuasive. The limited number of species disclosed is not deemed to be representative of the genus encompassed by the instant claims.

Furthermore although Examiner Navarro agreed to only take into consideration the experimental data on October 8, 2008. The *Staphylococcus aureus* experimental results already presented in the present specification do not provide enablement for a gram positive bacteria. The claims encompass any microbial pathogen which includes bacteria, viruses and fungi. Furthermore the instant claims are drawn to reducing the virulence of a microbial pathogen the claims and are not limited to the reduction in colonization. Therefore the experimental data as disclosed in the declaration on October 8, 2008 are not in commensurate in scope with the claims (see MPEP 716.02) and as such are deem non-persuasive.

As outlined previously: the specification, while being enabling for a method for attenuating the virulence of a microbial pathogen from *S. aureus* or for inhibiting or reducing colonization by a microbial pathogen from *S. aureus* in a patient in need thereof, comprising administering to the patient in need an effective amount of c-di-GMP, cGMP and 5'-GMP to attenuate the virulence of, or to inhibit or reduce colonization by, the microbial pathogen, does not reasonably provide enablement for any method for attenuating the virulence of any microbial pathogen or for inhibiting or reducing colonization by any microbial pathogen in a patient in need thereof,

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comprising administering to the patient in need an effective amount of c-di-GMP or a cyclic dinucleotide to attenuate the virulence of, or to inhibit or reduce colonization by, the microbial pathogen. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with the claimed invention.

Nature of the invention. The claims are drawn to any method for attenuating the virulence of a microbial pathogen or for inhibiting or reducing colonization by a microbial pathogen in a patient in need thereof, comprising administering to the patient in need an effective amount of c-di-GMP or a cyclic dinucleotide to attenuate the virulence of, or to inhibit or reduce colonization by, the microbial pathogen.

The breadth of the claims. The method claim is very broad and the product, a cyclic dinucleotides used to administer to a patient is directed to any microbial pathogen. Furthermore the claims are drawn to any method for attenuating the virulence of a microbial pathogen or for inhibiting or reducing colonization of a microbial pathogen in a patient in need thereof, comprising administering to the patient in need an effective amount of any cyclic dinucleotide to attenuate the virulence of, or to inhibit or reduce colonization by, the microbial pathogen. Therefore it is hard for one skilled in the art to determine if any cyclic dinucleotide can be used to attenuate the virulence, inhibit or reduce the colonization or any microbial pathogen in a patient. Since the specification fails to provide particular guidance for any method for attenuating the virulence of a microbial pathogen or for inhibiting or reducing colonization of a microbial pathogen in a patient in need thereof, comprising administering to the patient in need an effective amount of any type of a cyclic dinucleotide to attenuate the virulence of, or to inhibit or reduce colonization by, the microbial pathogen, it would require undue experimentation to practice the invention over the broad scope as presently claimed.

Guidance in the specification/Working Example. The specification discloses in Example 3 (see pp. 49-67), various examples, such as the effect of c-di-GMP on *S. aureus* biofilm formation (see 00101), the effects of c-di-GMP on *S. aureus* pre-formed biofilms (00102), c-di-

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GMP treatment that prevents cell to cell interaction (see 00111), c-di-GMP inhibiting biofilm formation in human and bovine *S. aureus* (see 00113), the effects of cGMP and 5'GMP on biofilm formation (see 00116), the effect of c-di-GMP treatment on *S. aureus* pre-formed biofilms (see 00117), and lastly safety and toxicity tests disclosing the treatment of c-di-GMP on mice that indicates to the inventor that c-di-GMP is relatively safe and not toxic (see 00119-00120). There is no showing in the specification that cyclic dinucleotides can be administered to a patient to attenuate the virulence of a microbial pathogen or for inhibiting or reducing colonization by a microbial pathogen. Although the specification gives several examples of a method for inhibiting microbial colonization and pre-formed microbial biofilm by disclosing various examples, such as in vitro studies of the effects c-di-GMP or any cyclic dinucleotides species thereof on pre-formed microbial biofilm or biofilm formation and c-di-GMP treatment that prevents cell to cell interaction (see Example 3), the specification fails to show a method comprising administering to the patient in need an effective amount of c-di-GMP or any cyclic dinucleotide to attenuate the virulence of, or to inhibit or reduce colonization by, the microbial pathogen. Furthermore although the specification discloses orally administering c-di-GMP to mice that indicates to the inventor that c-di-GMP is relatively safe and not toxic only contemplates the claimed invention (see 00119-00120). The specification does not give any working example (i.e. challenged mice models or passive immunization approaches). Therefore the specification fails to describe any method for attenuating the virulence of any microbial pathogen or for inhibiting or reducing colonization by any microbial pathogen in a patient in need thereof.

The state of the prior art. The state of the art is unpredictable with regard to administering cyclic dinucleotides to attenuate the virulence of a microbial pathogen or for inhibiting or reducing colonization in a patient. The state of the art questions the correlation between in vivo and in vitro models for treatment of bacterial/microbial pathogens. For example, Parsek et al proposed four basic criteria to define biofilm-associated infections: (i) Bacterial cell adherence to or association with a surface, (ii) in vivo observation of bacterial cell clusters, (iii) a localized infection pattern, and (iv) increased resistance to antibiotic treatment in the host compared to resistance of genetically equivalent planktonic bacteria. A role for bacterial biofilms in

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pathogenesis is well established for a number of infections and opportunistic pathogens; for many other infections a link between biofilms and disease has been proposed, but the evidence remains less clear (see Parsek et al 2003. Bacterial biofilms: an emerging link to disease pathogenesis. Annu. Rev. Microbiol. 57:677-701 in its entirety). The state of the art indicate that Reisner et al teach the understanding of *Escherichia coli* biofilm formation in vitro is based on studies of laboratory K-12 strains grown in standard media. The data demonstrate that prevalence and expression of three factors known to strongly promote biofilm formation in *E. coli* K-12 (F-like conjugative pili, aggregative adherence fimbriae, and curli) cannot adequately account for the increased biofilm formation of nondomesticated *E. coli* isolates in vitro. Reisner et al discuss the complexity of genetic and environmental effectors of the biofilm phenotype within the species *E. coli*. Reisner et al teach the results found were a poor correlation between biofilm formation in different media, suggesting that *E. coli* isolates respond very differently to the changing growth and environmental conditions and that this finding emphasizes the relevance and difficulty involved in selecting proper conditions for in vitro biofilm studies which attempt to mirror natural environments in vivo. Reisner et al teach that based the results, in vitro biofilm phenotypes cannot be correlated with the expected virulence phenotypes of the *E. coli* isolates in vivo. Reisner et al further teach that a tremendous impact of environmental conditions highlights the need to develop better biofilm model systems to approximate in vivo situations. Furthermore careful adjustment of the medium composition is an important first step. Incorporation of more adequate surfaces in the experimental design appears to be an additional measure, e.g., by studying biofilm formation directly on eukaryotic cells. However, given that multiple species are present in most environments, we also need to establish models that enable monitoring of possible antagonistic or synergistic interactions between community members (see Reisner et al 2006 Journal of Bacteriology Vol. 188 No. 10 pgs. 3572-3581 see abstract, pg. 3572 column 1 and pg. 3580). Furthermore the art indicates that device related infections are difficult to treat with antibiotics alone and that the minimum inhibitory concentrations (MICs) are not predictive for the therapeutic outcome in either the in vitro or in vivo model. For example the treatment of device related infections between the efficacy of antibiotics and the of drug levels of MICs is poor (see abstract and pg. 1138). Furthermore, the art indicates that the clinical relevance of susceptibility testing has always been questioned because of the difficulty of correlating in vitro

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susceptibility testing with in vivo clinical effectiveness and that there have always been host/pathogen factors that influence the clinical outcome that cannot be predicted by the results of susceptibility testing (see Stratton 2006 Med. Clin North Am Vol. 6 pgs. 1077-1088 see abstract). The state of the art teach that c-di-GMP is a novel naturally occurring nucleotide identified in prokaryotic systems and has found to be active in eukaryotic systems (see Steinberger et al 1999 FEBS LETTERS Vol. 444 pgs. 125-129 specifically pg. 125). Additionally Bowie et al (Science, 1990, 247:1306-1310) teach that an amino acid sequence encodes a message that determines the shape and function of a protein and that it is the ability of these proteins to fold into unique three-dimensional structures that allows them to function, carry out the instructions of the genome and form immunoepitopes. Bowie et al. further teach that the problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex. (column 1, page 1306). Bowie et al further teach that while it is known that many amino acid substitutions are possible in any given protein, the position within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of maintaining function are limited. Certain positions in the sequence are critical to the three dimensional structure/function relationship and these regions can tolerate only conservative substitutions or no substitutions (column 2, page 1306). Therefore the art questions whether any type of cyclic dinucleotides would have the same effect on the method as claimed.

Furthermore the art has not shown any method of administering any type of cyclic dinucleotides to attenuate the virulence of any microbial pathogen or for inhibiting or reducing colonization in a patient. The art questions the correlation between an in vivo and an in vitro model. Therefore, given the lack of success in the art. For the reasons set forth supra, the state of the art is unpredictable in regards to administering any cyclic dinucleotide to attenuate the virulence of any microbial pathogen or for inhibiting or reducing colonization in a patient.

In conclusion, the claimed inventions are not enabled for any method for attenuating the virulence of any microbial pathogen or for inhibiting or reducing colonization by any microbial pathogen in a patient in need thereof, comprising administering to the patient in need an effective amount of c-di-GMP or a cyclic dinucleotide to attenuate the virulence of, or to inhibit or reduce

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colonization by, the microbial pathogen. The state of the art indicates that the clinical relevance of susceptibility testing has always been questioned because of the difficulty of correlating in vitro susceptibility testing with in vivo clinical effectiveness and that there have always been host/pathogen factors that influence the clinical outcome that cannot be predicted by the results of susceptibility testing (see Stratton 2006 Med. Clin North Am Vol. 6 pgs. 1077-1088 see abstract). The art has not shown any method of administering c-di-GMP or any cyclic dinucleotide to attenuate the virulence of any microbial pathogen or for inhibiting or reducing colonization in a patient. Furthermore, the art questions the correlation between an in vivo and an in vitro model. For the reasons set forth supra, the state of the art is unpredictable. There is also a lack of working examples. Although the specification discloses orally administering c-di-GMP to mice that indicates to the inventor that c-di-GMP is relatively safe and not toxic only contemplates the claimed invention. As a result, for the reasons discussed above, it would require undue experimentation for one skilled in the art to use the claimed methods.

Enablement

4. The rejection of claims 17-21 under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement are maintained for the reason set forth in the previous office action. The claim(s) contain subject matter, which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Applicant arguments:

Applicants arguments filed in response to the 35 U.S.C. 112, first paragraph May 13, 2009 is carefully considered, but not found to be persuasive for the reasons below.

A) Applicants state that the examiner appears to take the position in this rejection that the amended claims reciting only for cyclic dinucleotides encompass any type of derivative of a cyclic dinucleotide, such as similarly maintained in the anticipation and lack of enablement rejections discussed above and as stated again here, the cyclic dinucleotides recited in the present claims do not encompass any type of derivative or analogue of cyclic dinucleotides but must be itself a cyclic dinucleotide. Applicants state that as discussed at the personal interview of August

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8, 2008, applicants' proposal to amend claims 17-21 from "microbial pathogens" to "bacterial pathogens" would be viewed favorably, according to Examiner Navarro, if a few examples with different bacterial species can be shown. Applicant has provided a copy of Mano et al., Chem. Med. Chem. 2:1410-1413 (2007), as evidence that cyclic dinucleotides, c-di-GMP and c-dGpGp, inhibited biofilm formation of three types of bacterial pathogens important in infections in humans.

Examiner's Response to Applicant's Arguments:

In response to applicant's statement, as stated in the previous office action, the method as instantly claimed encompasses all dinucleotides. Although a limited number of cyclic dinucleotides are disclosed in the specification, an although said cyclic dinucleotides were properly described is still not persuasive. The limited number of species disclosed is not deemed to be representative of the genus encompassed by the instant claims.

Furthermore Although Examiner Navarro agreed to take into consideration the proposal to amend claims 17-21 from "microbial pathogens" to "bacterial pathogens". However the proposal is not persuasive. The claims are not specifically limited to any type of bacteria and any type of infection. The claims encompass any bacteria and the instant claims are drawn to inhibiting bacterial colonization and biofilm formation or for reducing colonization and pre-formed bacterial biofilm on a solid surface and are not limited to the inhibiting biofilm formation. Finally, contrary to Applicant's assertion, Applicant has not provided a copy of Mano et al., Chem. Med. Chem. 2:1410-1413 (2007), as evidence that cyclic dinucleotides, c-di-GMP and c-dGpGp, inhibited biofilm formation of three types of bacterial pathogens important in infections in humans.

As outlined previously, the specification, while being enabling for a method for inhibiting *Staphylococcus aureus* (*S. aureus*) colonization and *S. aureus* biofilm formation or for reducing *S. aureus* colonization and pre-formed *S. aureus* microbial biofilm on a solid surface, comprising exposing the solid surface to an effective amount of c-di-GMP or a cyclic dinucleotide to inhibit *S. aureus* colonization and *S. aureus* biofilm formation or to reduce microbial colonization and pre-formed biofilm on said solid surface, does not reasonably provide enablement for any method for inhibiting bacterial colonization and biofilm formation or for reducing colonization and pre-

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formed bacterial biofilm on a solid surface, comprising exposing the solid surface to an effective amount of c-di-GMP or a cyclic dinucleotide to inhibit bacterial colonization and biofilm formation or to reduce bacterial colonization and pre-formed biofilm on said solid surface. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with the claimed invention.

Nature of the invention. The claims are drawn to for any method for attenuating the virulence of a microbial pathogen or for inhibiting or reducing colonization by a microbial pathogen in a patient in need thereof, comprising administering to the patient in need an effective amount of c-di-GMP or a cyclic dinucleotide to attenuate the virulence of, or to inhibit or reduce colonization by, the microbial pathogen.

The breadth of the claims. The method claim is very broad and the product, a c-di-GMP or any cyclic dinucleotide used in the method as set for supra to any type of microbial colonization or any type biofilm formation. Furthermore the claims are drawn to any method for inhibiting any type microbial colonization and any type of biofilm formation or for reducing any type of colonization and pre-formed any type of microbial biofilm on a solid surface, comprising exposing the solid surface to an effective amount of a c-di-GMP or any cyclic dinucleotide to inhibit any type of microbial colonization and any biofilm formation or to reduce any microbial colonization and any pre-formed biofilm on said solid surface. Therefore it is hard for one skilled in the art to determine if c-di-GMP or any cyclic dinucleotide can be used in the method as set forth supra. The quantity of experimentation required to practice the invention as claimed would require studies of c-di-GMP or any cyclic dinucleotide to attenuate the virulence of, or to inhibit or reduce colonization of all types of microbial pathogens. Since the specification fails to provide particular guidance for the method as set forth supra, it would require undue experimentation to practice the invention over the broad scope as presently claimed.

Guidance in the specification/Working Examples. The specification discloses in Example 3 (see pp. 49-67), various examples, such as the effect of c-di-GMP on *S. aureus* biofilm formation (see

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00101), the effects of c-di-GMP on *S. aureus* pre-formed biofilms (00102), c-di-GMP treatment the prevents cell to cell interaction (see 00111), c-di-GMP inhibiting biofilm formation in human and bovine *S. aureus* (see 00113), the effects of cGMP and 5'GMP on biofilm formation (see 00116), the effect of c-di-GMP treatment on *S. aureus* pre-formed biofilms (see 00117), and lastly safety and toxicity tests disclosing the treatment of c-di-GMP on mice that indicates to the inventor that c-di-GMP is relatively safe and not toxic (see 00119-00120). The specification gives several examples of *S. aureus* bacteria in method for inhibiting microbial colonization and pre-formed microbial biofilm by disclosing various examples, such as in vitro studies of the effects c-di-GMP or any cyclic dinucleotide on pre-formed microbial biofilm or biofilm formation and c-di-GMP treatment that prevents cell to cell interaction (see Example 3. Furthermore Example 4 discloses extracellular c-di-GMP increases. Furthermore although the specification discloses orally administering c-di-GMP to mice that indicates to the inventor that c-di-GMP is relatively safe and not toxic only contemplates the claimed invention (see 00119-00120). Therefore the specification fails to describe any method for attenuating the virulence of a microbial pathogen or for inhibiting or reducing colonization by a microbial pathogen in a patient in need thereof, comprising administering to the patient in need an effective amount of c-di-GMP or a cyclic dinucleotide to attenuate the virulence of, or to inhibit or reduce colonization by, the microbial pathogen.

The state of the prior art. The state of the art is unpredictable with regard to c-di-GMP and inhibiting or reducing colonization and biofilm formation in microbial pathogens. state of the art teach that c-di-GMP is a novel naturally occurring nucleotide identified in prokaryotic systems and has found to be active in eukaryotic systems (see Steinberger et al 1999 FEBS LETTERS Vol. 444 pgs. 125-129 specifically pg. 125). Parsek et al proposed four basic criteria to define biofilm-associated infections: (i) Bacterial cell adherence to or association with a surface, (ii) in vivo observation of bacterial cell clusters, (iii) a localized infection pattern, and (iv) increased resistance to antibiotic treatment in the host compared to resistance of genetically equivalent planktonic bacteria. A role for bacterial biofilms in pathogenesis is well established for a number of infections and opportunistic pathogens; for many other infections a link between biofilms and disease has been proposed, but the evidence remains less clear (see Parsek et al 2003. Bacterial

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biofilms: an emerging link to disease pathogenesis. *Annu. Rev. Microbiol.* 57:677-701 in its entirety). The state of the art indicate that Reisner et al teach the understanding of *Escherichia coli* biofilm formation in vitro is based on studies of laboratory K-12 strains grown in standard media. The data demonstrate that prevalence and expression of three factors known to strongly promote biofilm formation in *E. coli* K-12 (F-like conjugative pili, aggregative adherence fimbriae, and curli) cannot adequately account for the increased biofilm formation of nondomesticated *E. coli* isolates in vitro. Reisner et al discuss the complexity of genetic and environmental effectors of the biofilm phenotype within the species *E. coli*. Reisner et al teach the results found were a poor correlation between biofilm formation in different media, suggesting that *E. coli* isolates respond very differently to the changing growth and environmental conditions and that this finding emphasizes the relevance and difficulty involved in selecting proper conditions for in vitro biofilm studies which attempt to mirror natural environments in vivo. Reisner et al teach that based the results, in vitro biofilm phenotypes cannot be correlated with the expected virulence phenotypes of the *E. coli* isolates in vivo. Reisner et al further teach that a tremendous impact of environmental conditions highlights the need to develop better biofilm model systems to approximate in vivo situations. Furthermore careful adjustment of the medium composition is an important first step. Incorporation of more adequate surfaces in the experimental design appears to be an additional measure, e.g., by studying biofilm formation directly on eukaryotic cells. However, given that multiple species are present in most environments, we also need to establish models that enable monitoring of possible antagonistic or synergistic interactions between community members (see Reisner et al 2006 *Journal of Bacteriology* Vol. 188 No. 10 pgs. 3572-3581 see abstract, pg. 3572 column 1 and pg. 3580). Furthermore the art indicates that device related infections are difficult to treat with antibiotics alone and that the minimum inhibitory concentrations (MICs) are not predictive for the therapeutic outcome in either the in vitro or in vivo model. For example the treatment of device related infections between the efficacy of antibiotics and the of drug levels of MICs is poor (see abstract and pg. 1138). Furthermore, the art indicates that the clinical relevance of susceptibility testing has always been questioned because of the difficulty of correlating in vitro susceptibility testing with in vivo clinical effectiveness and that there have always been host/pathogen factors that influence the clinical outcome that cannot be predicted by the results

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of susceptibility testing (see Stratton 2006 Med. Clin North Am Vol. 6 pgs. 1077-1088 see abstract).

The art questions biofilm model systems and the factors that have to be considered as set forth supra. Therefore, given the lack of success in the art the state of the art is unpredictable with regard to c-di-GMP and inhibiting or reducing colonization and biofilm formation in microbial pathogens.

In conclusion, the claimed invention is not enabled for any method for inhibiting bacterial colonization and biofilm formation or for reducing colonization and pre-formed bacterial biofilm on a solid surface, comprising exposing the solid surface to an effective amount of c-di-GMP or a cyclic dinucleotide to inhibit bacterial colonization and biofilm formation or to reduce bacterial colonization and pre-formed biofilm on said solid surface. The state of the art indicates that the clinical relevance of susceptibility testing has always been questioned because of the difficulty of correlating in vitro susceptibility testing with in vivo clinical effectiveness and that there have always been host/pathogen factors that influence the clinical outcome that cannot be predicted by the results of susceptibility testing (see Stratton 2006 Med. Clin North Am Vol. 6 pgs. 1077-1088 see abstract). The art questions biofilm model systems and the factors that have to be considered as set forth supra. Therefore, given the lack of success in the art the state of the art is unpredictable with regard to c-di-GMP and inhibiting or reducing colonization and biofilm formation in microbial pathogens. As a result, for the reasons discussed above, it would require undue experimentation for one skilled in the art to use the claimed methods.

Conclusion

5. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nina A. Archie whose telephone number is 571-272-9938. The examiner can normally be reached on Monday-Friday 8:30-5:00p.m.

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If attempts to reach the examiner by telephone are unsuccessful, the examiner supervisor, Robert Mondesi can be reached on 571-272-0956. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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Nina A Archie

Examiner

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REM 3B31

/Robert A. Zeman/

for Nina Archie, Examiner of Art Unit 1645